

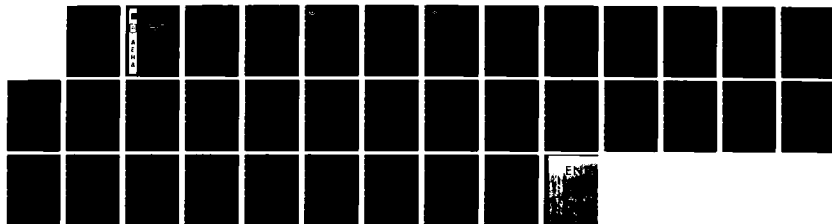
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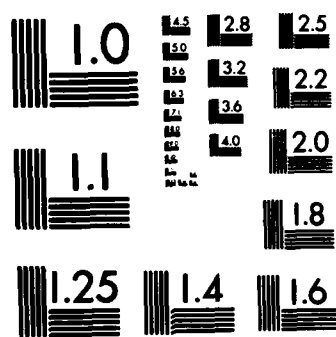
TOXICOLOGICAL ASSESSMENT OF ABATE (TRADE NAME)
(000'0'-TETRAMETHYL-00'-TH. (U) ARMY ENVIRONMENTAL
HYGIENE AGENCY ABERDEEN PROVING GROUND MD
R A ANGERHOFER ET AL. 27 SEP 83

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**UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY**

ABERDEEN PROVING GROUND, MD 21010

PHASE 3
STUDY NO. 75-51-1302-83
TOXICOLOGICAL ASSESSMENT OF ABATE®
(O,O,O',O'-TETRAMETHYL-O,O'-THIO-DI-P-PHENYLENE PHOSPHOROTHIOATE)
ADMINISTERED ORALLY TO MATED AND NONMATED FEMALE RABBITS
APRIL 1983

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER 75-51-1302-83	2. GOVT ACCESSION NO. AD-A133 154	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Phase 3, Toxicological Assessment of ABATE (0,0,0',0'-Tetramethyl-0,0'-Thio-di-p-Phenylene Phosphorothioate) Administered Orally to Mated and Nonmated Female Rabbits, Study No. 75-51-1302-83, April 1983		5. TYPE OF REPORT & PERIOD COVERED Interim, Sep 1979 - Aug 1983
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) This study was designed to assess the embryotoxic and teratologic potential of ABATE following repeated oral administration of the compound to pregnant rabbits during the period of gestation which spans organogenesis. Mated and nonmated animals were used in order to compare the toxic effects of ABATE in combination with the stress of pregnancy. These tests indicated no teratologic effects in New Zealand White Rabbits following repeated oral administration of ABATE at levels which produced a toxic effect. The stress of pregnancy did not produce an increased sensitivity to the compound. Although these studies have shown		

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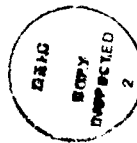
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20. that ABATE should not cause teratologic effects in its intended use, chronic studies should be performed to further define any potential long term toxicity.

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DEPARTMENT OF THE ARMY Mr. Angerhofer/jr/AUTOVON
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY 584-3980
ABERDEEN PROVING GROUND, MARYLAND 21010

REPLY TO
ATTENTION OF

HSHB-LT-T/WP

27 SEP 1983

SUBJECT: Phase 3, Study No. 75-51-1302-83, Toxicological Assessment of
ABATE® (0,0,0',0'-Tetramethyl-0,0'-Thio-Di-P-Phenylene
Phosphorothioate) Administered Orally to Mated and Nonmated Female
Rabbits, April 1983

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20307

EXECUTIVE SUMMARY

The purpose, essential findings and major recommendations of the inclosed report follow:

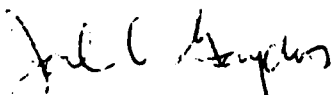
a. Purpose. The purpose of this study was to assess the embryotoxic and teratologic potential of ABATE® following repeated oral administration of the compound to pregnant rabbits during the critical period of gestation. Mated and nonmated animals were used in order to compare the toxic effects of ABATE in combination with the stress of pregnancy.

b. Essential Findings. These tests indicated no teratologic effects in New Zealand White rabbits following repeated oral administration of ABATE at levels which produced a toxic effect. The stress of pregnancy did not produce an increased sensitivity to the compound.

c. Major Recommendations. Although these studies have shown that ABATE should not cause teratologic effects in its intended use, chronic studies should be performed to further define any potential long term toxicity.

FOR THE COMMANDER:

1 Incl
as


JOEL C. GAYDOS, M.D.
Colonel, MC
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Environmental Health

CF:
HQDA (DASG-PSP) wo incl
Cdr, HSC (HSPA-P)
Comdt, AHS (HSHA-IPM)
Dir, Advisory Ctr Div Tox, NRC (2 cy)
USDA, ARS, Southern Region (3 cy)
USDA, ARS, Southern Region (LTC Reinert)
USDA, ARS (Dr. Terrence McGovern)

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

REPLY TO
ATTENTION OF
HSE-LT-T/WP

PHASE 3
STUDY NO. 75-51-1302-83
TOXICOLOGICAL ASSESSMENT OF ABATE®
(0,0,0',0'-TETRAMETHYL-0,0'-THIO-DI-P-PHENYLENE PHOSPHOROTHIOATE)
ADMINISTERED ORALLY TO MATED AND NONMATED FEMALE RABBITS
APRIL 1983

1. AUTHORITY. Letter, HSPA-H, US Army Health Services Command, 20 October 1976, subject: Investigational New Drug Application for ABATE Pediculicide, with inclosure, letter, AFPCB, Armed Forces Pest Control Board, 13 September 1976, same subject.

2. REFERENCE. Memorandum for Record, SGRD-UWF-B, Walter Reed Army Institute of Research, 18 July 1978, subject: ABATE Pediculicide.

3. SUMMARY AND CONCLUSIONS. Studies were conducted to evaluate the potential for ABATE to produce embryotoxic or teratogenic effects in pregnant rabbits after oral administration from the 6th through 18th day of pregnancy. The compound preparations and oral dosages used in this study were:

Technical grade ABATE in 10
percent acacia: mated rabbits 32 mg/kg/day

Technical grade ABATE in 10
percent acacia: nonmated rabbits 32 mg/kg/day

Acacia, 10 percent in distilled
water: mated rabbits 0.36 ml/kg/day

Acacia, 10 percent in distilled
water: nonmated rabbits 0.36 ml/kg/day

Under the conditions of the experiment, the following parameters were found to be affected:

a. Technical grade ABATE in acacia, 32 mg/kg/day, produced deaths in both mated and nonmated rabbits. The stress of pregnancy did not produce an increased sensitivity to the compound.

b. Technical grade ABATE in acacia, 32 mg/kg/day, produced significantly reduced RBC, plasma and brain cholinesterase activity in surviving mated and nonmated rabbits.

c. These tests indicated no teratologic hazard in New Zealand White rabbits following repeated oral administration of ABATE at levels that produced a toxic effect in adult rabbits.

®ABATE is a registered tradename for American Cyanamid Co., Princeton, New Jersey.

Use of trademarked names does not imply endorsement by the US Army, but is intended only to assist in identification of a specific product.

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d. Although these studies have shown that ABATE should not cause teratological effects in its intended use, it is recommended that chronic studies be performed to further define any potential long term toxicity.

4. BACKGROUND.

a. The Armed Forces Pest Management Board (AFPMB), formerly the Armed Forces Pest Control Board, is coordinating the registration of ABATE as a pediculicide with the Food and Drug Administration (FDA), since a formulation of this compound is proposed for standardization for the control of lice in military programs. Negotiations with FDA for a field test program for this preparation have indicated the need for the development of an Investigational New Drug Application (IND). The only formulation for which FDA registration is to be sought is 2 percent ABATE, 98 percent Pyrax®. The target species are:

- (1) The body louse, Pediculus humanus humanus (L.)
- (2) The head louse, Pediculus humanus cepitis (DeGeer)
- (3) The pubic louse, Phthirus pubis (L.)

b. To assist in the development of this IND, the US Army Environmental Hygiene Agency (USAEHA) was requested to conduct a teratology study in a second mammalian species, namely the rabbit (see paragraph 1, this report).

c. The proposed patterns of use for 2 percent ABATE pediculicide encompass both group and individual treatment. The group method involves the treatment of infested individuals by operators using power-driven or manually-operated equipment. It is estimated that the group application method results in the application of approximately 31 gm of formulated dust (0.62 gm active ingredient) per individual.

d. The individual treatment method involves self-treatment of individuals. For this purpose, the dust is packaged in 2 oz (56.7 gm) shaker cans. Instructions will indicate that the entire contents of the can be used for heavy infestations, and the amount to be applied may thus be assumed to be 56.7 gm of formulated powder (1.13 gm active ingredient).

e. Initial teratological studies in rabbits, Groups I - IX, utilizing both dermal and oral applications to pregnant females, showed no evidence of teratogenicity. Lack of a workable oral dosing technique led to many female deaths (7/15) which were not compound related. For this reason, it was decided to repeat the oral portion of the study and to add groups of normated controls¹. The oral dose of 32 mg/kg was based on a preliminary range finding study in rabbits. In that study, several concentrations of ABATE in 10 percent acacia were given daily by the oral route in an attempt to lower plasma and RBC cholinesterase values to approximately 50 percent of pretreatment levels.

f. The bibliography is presented in Appendix W.

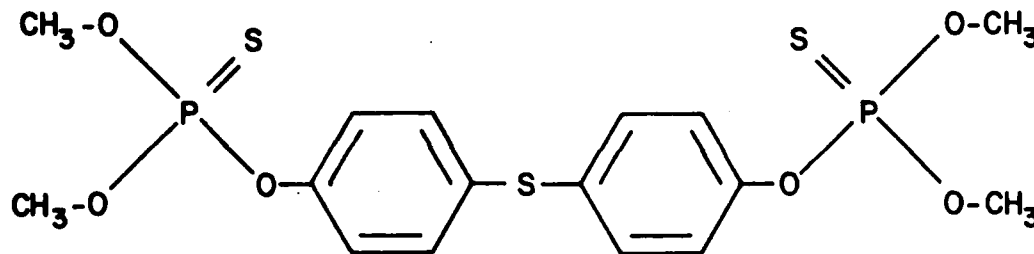
®Pyrax is a registered trademark of R. T. Vanderbilt Company, Inc., New York, NY 10017.

5. **PURPOSE.** The purpose of this study was to assess the embryotoxic and teratologic potential of ABATE following repeated oral administration of the compound to pregnant rabbits during the critical period of gestation. The study was designed in accordance with the 1966 "Guidelines for Reproduction Studies for Safety Evaluations of Drugs for Human Use" distributed by FDA. Mated and nonmated animals were used in order to compare the toxic effects of ABATE in combination with the stress of pregnancy.

6. **MATERIALS AND METHODS.**

a. Chemicals.

(1) The experimental insecticide ABATE (0,0,0',0'-tetramethyl-0,0'-thio-di-p-phenylene phosphorothioate) CAS Number 003383-96-8, is a reddish amber viscous liquid, $d_{25} = 1.587$, with a foul odor. It is also identified or known as Bithion, Difenthos, ENT-27165, Experimental Insecticide 52160, and Temephos. It is soluble in acetonitrile, carbon tetrachloride, ether, ethylene dichloride and toluene. It is insoluble in hexane, methyl cyclohexane and water. The molecular weight is 466.48; its empirical formula is $C_{16}H_{20}O_6P_2S_3$ and its structural formula is shown below:



(2) The material used in these studies was supplied by American Cyanamid Company, Agricultural Division, Princeton, New Jersey, and was contained in a labeled plastic bottle. The label contained a warning statement and the name ABATE, Technical Insecticide, Active Ingredients: Temephos [0,0'(thiodi-4, 1-phenylene) bis(0, 0-dimethyl phosphorothioate)] 90 percent W/W, Inert Ingredients 10 percent and lot identification number L3402 R3 6/76 WG.

(3) Acacia, U.S.P. (Gum Arabic) - F.C.C., Food Grade (No. 5-0430, Lot No. 421152), was procured from J. T. Baker Chemical Co., Phillipsburg, NJ 08865.

b. Animals. Two groups of 30 sexually mature female New Zealand White rabbits were purchased from Dutchland Laboratory Animals, Inc., Denver, Pennsylvania, and were received in two shipments, 4 weeks apart. Half of each group (15) were purchased as dated pregnant females. The day of mating was defined as Day 0 of gestation and the impregnated rabbits were received on Day 1 of gestation along with the normated rabbits of that group. Rabbits were housed in individual cages (Porter-Mathews, 16 inches x 18 inches x 24 inches) and received a laboratory diet (Rabbit Chow Checkers, Ralston Purina Co., St Louis, MO 63188) and tap water ad libitum throughout the test. The room temperature was kept at 23°C, relative humidity 45-55 percent, and the lighting period was 12 hours daily.

c. Test Solution and Treatment Schedule.

(1) Technical grade ABATE was suspended in 10 percent aqueous acacia to a final concentration of 90 mg/mL. Oral administration of ABATE to test animals was always 32 mg/kg/day. This dose was selected from preliminary range finding tests because it produced significant cholinesterase depression in rabbits following repeated oral administration.

(2) In accordance with the FDA guidelines mentioned previously, mated female rabbits were dosed daily from day 6 through day 18 of pregnancy. Normated test rabbits were similarly treated. Control females, mated and normated, followed the same treatment regimen, but received only 10 percent aqueous acacia in comparable volumes (0.36 mL/kg/day). Dosages were adjusted daily according to individual body weights. The experimental design is shown in Appendix A.

d. Test Procedure.

(1) Mated rabbits were received on Day 1 of gestation. Treatment was initiated on Day 6 and continued through Day 18 of gestation. Administration of the compound or diluent was made by intragastric intubation. Daily observation of toxicological signs were noted. All animals were weighed on Days 5-19 and Days 26 and 30. Animals were bled from the central ear artery at certain intervals during the study for determination of plasma and erythrocyte (RBC) cholinesterase activity. These analyses were performed according to the method described by Garry and Routh¹. All animals were sacrificed on Day 30 of gestation by an overdose of pentobarbital. At this time, the brains of all does were removed for brain cholinesterase activity determination.

(2) The examination of fetuses for malformations was conducted according to the method of Wilson and Warkany². The postmortem for each doe consisted of counting the conceptuses: number, location, living, dead, early resorptions and late resorptions. All fetuses were tagged for identification, weighed, measured and examined for external defects. Approximately one-half of the fetuses were fixed in Bouin's fluid³ and examined by the Wilson technique for neural and visceral defects². The remaining fetuses were placed in 95 percent ethyl alcohol, cleared and their skeletons stained with alizarin red S and examined for malformations⁴.

7. RESULTS.

a. Evaluation of Data.

(1) Definition of Terms. The following indices were calculated; A summary of results appears in Appendices B through D.

$$\text{Index of fertility: } \frac{\text{pregnant animals}}{\text{total number of mated animals}} \times 100$$

$$\text{Index of viable births: } \frac{\text{alive normal fetuses}}{\text{total number of fetuses}} \times 100$$

$$\text{Index of dead births: } \frac{\text{dead normal fetuses}}{\text{total number of fetuses}} \times 100$$

$$\text{Index of resorptions: } \frac{\text{total number of resorptions}}{\text{total number of implantations}} \times 100$$

$$\text{Index of variations: } \frac{\text{total number of variations}}{\text{total number of fetuses}} \times 100$$

$$\text{Index of malformations: } \frac{\text{total number of malformations}}{\text{total number of fetuses}} \times 100$$

Variations: all runts and anomalies

Early resorptions: placental remains only

Late resorptions: placental and embryonic remnants

Runts: animals weighing 70 percent or less of the average weight of each litter.

(2) Statistical Analysis. Applicable fetal parameters, cholinesterase values and body weights were analyzed statistically using the Student's "t" test with significance selected at the 0.05 level of probability.

b. Maternal Parameters.

(1) Clinical Picture of Females. Mated and nonmated animals of both groups were received in good condition as judged by the attending veterinarian and showed a smooth, shiny hair coat.

(2) Weight Gain of Females. Body weights of control animals remained essentially unchanged or gained slightly during the treatment

Phase 3, Toxicological Assessment of ABATE, Study No. 75-51-1302-83, Apr 83

period. Nonmated rabbits given technical ABATE orally showed slight body weight losses toward the end of the treatment period. Surviving animals recovered this weight loss by the time of sacrifice. Maternal body weight data are presented in Appendices E through I.

(3) Toxicity.

(a) Oral administration of technical grade ABATE at 32 mg/kg/day (X 13 days) in 10 percent aqueous acacia caused a significant reduction in RBC and plasma cholinesterase activity in both mated and nonmated rabbits. Brain cholinesterase levels were similarly depressed in the same animals when compared to their acacia control counterparts at the end of the test. Cholinesterase levels of acacia control groups varied little from their pretest values except for the mated acacia control group which showed an unexplained plasma cholinesterase depression throughout the test period. This anomaly, however, was not perpetuated in either brain or RBC cholinesterase values for the same rabbits. Cholinesterase values are presented in Appendices J through V.

(b) Many of the rabbits which had received ABATE became anorexic at the end of the dosing period. One mated and two nonmated animals became ataxic at this time and died several days later.

(4) Necropsy Findings. None of the does sacrificed on the 30th day of pregnancy showed any sign of gross pathology at necropsy. No gross changes in tissues and organs of the female rabbits were found at necropsy.

c. Fetal Parameters.

(1) Index of Dead and Live-Born Fetuses. All fully developed fetuses were found to be viable at time of necropsy.

(2) Implantations - Resorptions - Number of Fetuses. No differences of biological relevance were found between test and control groups.

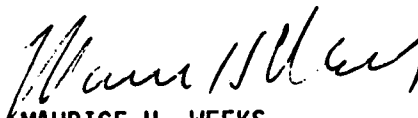
(3) Abnormalities/Anomalies. All true malformations (soft tissue and skeletal defects such as gastroschisis, cranioschisis, cleft palate) are defined as abnormalities. Anomalies are considered to be minor variants from the normal, such as unossified sternebrae or retarded ossification of the fontanella. No abnormalities were found in either the test or control group of fetuses. Very few anomalies (variants) were found and no differences of biological relevance were found between the two groups.

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(4) Average Fetal Weight. There was no significant difference between the average weight of fetuses from ABATE-treated animals and from animals receiving acacia only.



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Biologist
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Chief, Toxicology Division

Phase 3, Toxicological Assessment of ABATE, Study No. 75-51-1302-83, Apr 83

APPENDIX A

EXPERIMENTAL DESIGN

Treatment	Formulation Dosage	ABATE Dosage	Treatment Schedule (Days of Gestation)	No. of Rabbits
Mated Exposed; oral suspension of technical grade ABATE in aqueous 10% acacia	32 mg/kg/day	32 mg/kg/day	6-18	14
Non-mated Exposed; oral suspension of technical grade ABATE in aqueous 10% acacia	32 mg/kg/day	32 mg/kg/day	6-18 (equivalent)	15
Mated Control; oral aqueous solution of 10% acacia	0.36 ml/kg/day	--	6-18	15
Non-mated Control; oral aqueous solution of 10% acacia	0.36 ml/kg/day	--	6-18 (equivalent)	15

APPENDIX B

SUMMARY OF MATERNAL AND FETAL PARAMETERS

	Oral Control (10% Acacia) XI	Oral ABATE (32 mg/kg/day) X
Females Mated	15	14
Fatalities	0	1
Delivered Early (full term)	2	0
Females at Sacrifice	13	13
Females Pregnant	11	9
Fertility Index (%)	85	69
Litters	11	9
Gestation Index (%)	100	100
Implantations, Total	80	72
Implantations per Doe	7.27	8.00
Fetuses, Total	73	64
Fetuses, Per Doe	6.64	7.11
Alive Fetuses, Total	73	64
Alive Fetuses Per Doe	6.64	7.11
Index of Alive Fetuses (%)	100	100
Dead Fetuses, Total	0	0
Dead Fetuses Per Doe	0	0
Index of Dead Born Fetuses (%)	0	0
Resorptions, Total	7	8
Resorption Per Doe	0.64	0.89
Resorption Index (%)	8.75	11.11
Early resorption	7	8
Late resorptions	0	0
Variants, Total	2	1
Variants Per Doe	0.18	0.11
Index of Variants (%)	2.74	1.56
Malformations, Total	0	0
Malformation Index (%)	0	0
Runts	1	0
Average Fetal Weight (g)	46.00 +7.39	42.86 +6.30

APPENDIX C

MATERNAL AND FETAL PARAMETERS
INDIVIDUAL DATA GROUP X
ORAL ABATE - 32 mg/kg/day

Animal No.	Mated	Pregnant	Implantations	Resorptions Total No.			Dead	Alive	Malformation
				Early	Late	of Fetuses			
773	+	-							
774	+	+	12	3	0	9	0	9	0
775	+	+	9	0	0	9	0	9	0
776	+	+	6	1	0	5	0	5	0
777	+	-							
778	+	-							
779	+	-							
780	+	+	8	0	0	8	0	8	0
781	+	+	9	3	0	6	0	6	0
782	+	+	7	0	0	7	0	7	0
783	+	+	10	0	0	10	0	10	0
784	+	+	5	0	0	5	0	5	0
785	+	+	6	1	0	5	0	5	0
786	+	Died before term							

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APPENDIX D

MATERNAL AND FETAL PARAMETERS
INDIVIDUAL DATA - GROUP XII
ORAL - 10 PERCENT GUM ACACIA CONTROL

Animal No.	Mated	Pregnant	Implantations	Resorptions Total No.			Dead	Alive	Malformations
				Early	Late	of Fetuses			
728	+	+	10	0	0	10	0	10	0
729	+	+	5	3	0	2	0	2	0
730	+	+	9	0	0	9	0	9	0
731	+	-							
732	+	+	9	0	0	9	0	9	0
733	+	+	2	0	0	2	0	2	0
734	+	-							
735	+	+	11	0	0	11	0	11	0
736	+	+	7	0	0	7	0	7	0
737	+	+	9	0	0	9	0	9	0
738	+	+	8	0	0	8	0	8	0
739	+	+	2	1	0	1	0	1	0
740	+	+	8	3	0	5	0	5	0

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APPENDIX E
MEAN BODY WEIGHTS(kg) - FEMALE RABBITS

Group	Treatment	DAY OF GESTATION					
			Day 1 Day Received	Day 6 Treatment Starts	Day 9	Day 18 Final Treatment	Day 30 Sacrifice
X	Oral Technical ABATE (Mated)	\bar{x} +SD	3.3 0.5	3.4 0.5	3.5 0.5	3.6 0.5	3.7 0.5
XI	Oral Technical ABATE (Non-mated)	\bar{x} +SD	3.2 0.2	3.3 0.2	3.3 0.2	3.4 0.2	3.7 0.1
XII	Oral 10 Percent Acacia (Mated)	\bar{x} +SD	3.2 0.4	3.4 0.4	3.4 0.4	3.7 0.4	3.9 0.5
XIII	Oral 10 Percent Acacia (Non-mated)	\bar{x} +SD	2.2 0.2	2.4 0.2	2.5 0.2	2.7 0.2	3.1 0.4

Phase 3, Toxicological Assessment of ABATE, Study No. 75-51-1302-83, Apr 83

APPENDIX F
INDIVIDUAL MATERNAL BODY WEIGHTS (kg)
ABATE, 32 mg/kg/day, ORAL, GROUP X
MATED

Animal Number	DAY 1	DAY 5	DAY 6 Treat- ment starts	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 16	DAY 17	DAY 18 Final Treat- ment	DAY 19	DAY 26	DAY 30
773	3.1	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.3	3.3	3.2	3.2	3.4	3.5
774	4.7	4.8	4.7	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.9	4.9	4.9	4.9	6.0	5.0
775	3.0	3.2	3.2	3.2	3.3	3.3	3.2	3.3	3.3	3.4	3.4	3.5	3.5	3.5	3.4	3.4	3.7	3.8
776	3.1	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.4	3.4	3.4	3.4	3.3	3.1	3.1	3.2
777	2.9	3.0	2.9	3.1	3.0	3.0	3.0	3.1	3.1	3.1	3.1	3.1	3.1	3.1	3.2	3.1	3.2	3.3
778	3.4	3.5	3.5	3.5	3.6	3.5	3.5	3.6	3.6	3.6	3.7	3.7	3.7	3.8	3.8	3.7	3.9	4.0
779	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.7	3.7	3.7	3.7	3.8	3.8	3.8	3.7	3.6	3.8	3.9
780	3.0	2.9	2.8	2.9	2.9	2.9	2.9	3.0	3.0	3.0	3.0	3.0	3.1	3.1	3.1	3.0	3.2	3.3
781	2.9	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.1	3.1	3.1	3.2	3.2	3.2	3.2	3.0	3.3	3.3
782	3.4	3.4	3.3	3.4	3.4	3.4	3.4	3.4	3.5	3.5	3.5	3.6	3.6	3.6	3.6	3.6	3.8	3.7
783	3.5	3.7	3.7	3.8	3.8	3.9	3.9	4.0	4.0	4.1	4.1	4.2	4.2	4.2	4.2	4.2	4.2	4.0
784	3.0	3.2	3.2	3.2	3.3	3.3	3.2	3.3	3.3	3.4	3.4	3.5	3.5	3.5	3.5	3.3	3.6	3.6
785	3.2	3.3	3.2	3.3	3.3	3.3	3.4	3.4	3.4	3.4	3.4	3.4	3.5	3.5	3.5	3.4	3.6	3.6
786	3.6	3.9	3.9	4.0	4.0	4.0	4.0	4.1	4.1	4.1	4.2	4.3	4.3	4.3	4.3	4.2	Dead 17 Oct	
\bar{x}	3.3	3.4	3.4	3.5	3.5	3.5	3.5	3.5	3.5	3.6	3.6	3.6	3.7	3.7	3.6	3.6	3.7	3.7
$\pm SD$	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.6	0.5	0.5

**INDIVIDUAL BODY WEIGHTS (kg)
ABATE 32 mg/kg/day, ORAL, GROUP XI
NONMATED**

G-1

[illegible]

Phase 3, Toxicological Assessment of ABATE, Study No. 75-51-1302-83, Apr 83

APPENDIX H
INDIVIDUAL MATERNAL BODY WEIGHTS (kg)
10 PERCENT ACACIA, 0.36 ml/kg/day
ORAL, GROUP XII
MATED

Animal Number	DAY	DAY	DAY	DAY	DAY	DAY	DAY	DAY	DAY	DAY	DAY	DAY	DAY	DAY	DAY	DAY	DAY	DAY
	1	5	6	7	8	9	10	11	12	13	13	15	16	17	18	19	26	30
	DAY OF GESTATION																	
	Treat- ment starts																	
728	3.6	3.8	3.9	3.8	3.9	3.9	4.0	4.0	4.0	4.0	4.0	4.1	4.1	4.1	4.1	4.1	4.1	4.1
729	3.3	3.2	3.3	3.4	3.4	3.5	3.6	3.6	3.6	3.8	3.8	3.8	3.9	3.9	3.9	3.8	3.9	3.9
730	2.9	3.1	3.0	2.9	3.0	3.0	3.1	3.1	3.3	3.3	3.3	3.3	3.3	3.2	3.2	3.3	3.4	3.5
731	3.0	3.1	3.1	3.2	3.2	3.3	3.4	3.4	3.6	3.5	3.5	3.6	3.7	3.7	3.8	3.8	4.1	4.2
732	3.5	3.7	3.8	3.9	3.9	3.9	3.9	4.0	4.0	4.0	4.2	4.2	4.2	4.2	4.2	4.2	4.3	4.5
733	3.3	3.7	3.7	3.7	3.7	3.8	3.8	3.9	4.0	4.0	4.0	4.0	4.1	4.2	4.0	4.1	4.4	4.3
734	2.6	2.8	2.8	2.8	2.9	2.9	3.0	3.0	3.1	3.0	3.0	3.1	3.2	3.2	3.2	3.2	3.3	3.4
735	3.5	3.7	3.7	3.7	3.8	3.9	3.9	3.9	4.1	4.0	4.1	4.2	4.3	4.3	4.3	4.3	4.5	4.7
736	2.6	2.6	2.7	2.7	2.7	2.7	2.8	2.8	2.8	2.8	2.8	2.9	2.9	3.1	3.0	3.0	3.1	3.1
737	3.2	3.4	3.5	3.5	3.5	3.5	3.5	3.5	3.6	3.6	3.7	3.7	3.7	3.7	3.7	3.8	3.8	3.7
738	3.5	3.8	3.8	3.8	3.8	3.7	3.7	3.7	3.8	3.8	3.8	4.0	4.0	4.0	4.0	4.0	4.1	3.9
739	3.0	3.1	3.2	3.3	3.4	3.4	3.4	3.4	3.5	3.6	3.6	3.7	3.7	3.7	3.8	3.8	3.9	4.0
740	2.8	3.0	3.0	3.0	3.1	3.1	3.0	3.0	3.0	2.9	3.0	3.0	3.0	3.1	3.1	3.1	3.2	3.3
\bar{x}	3.2	3.3	3.4	3.4	3.4	3.4	3.5	3.5	3.6	3.6	3.6	3.7	3.7	3.7	3.7	3.7	3.9	3.9
+SD	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.4	0.4	0.4	0.5	0.5

APPENDIX I

INDIVIDUAL MATERNAL BODY WEIGHTS (kg)
10 PERCENT ACACIA, 0.36 ml/kg/day
ORAL, GROUP XIII
NONMATED

Animal Number	DAY 1	DAY 5	DAY 6 Treat- ment Starts	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 16	DAY 17	DAY 18 Final Treat- ment	DAY 19	DAY 20	DAY 21	DAY 22	DAY 23	DAY 24	DAY 25	DAY 26	DAY 27	DAY 28	DAY 29	DAY 30
713	2.1	2.2	2.2	2.2	2.3	2.3	2.3	2.3	2.3	2.4	2.4	2.5	2.5	2.5	2.6	2.6	2.7	2.8	2.8	2.8	2.8	2.8	2.7	2.7	2.8	2.8	2.8
714	2.1	2.3	2.3	2.3	2.4	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.7	2.7	2.7	2.7	2.7	2.8	2.8	2.8	2.8	2.8	2.7	2.7	2.8	2.8	2.8
715	2.2	2.4	2.5	2.5	2.4	2.4	2.5	2.5	2.5	2.7	2.6	2.8	2.8	2.8	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7
716	2.2	2.4	2.3	DEAD 28 Aug																							
717	2.3	2.5	2.4	2.4	2.3	2.3	2.4	2.5	2.5	2.6	2.6	2.6	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7
718	2.3	2.3	2.4	2.5	2.6	2.6	2.7	2.7	2.7	2.8	2.8	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
719	2.4	2.5	2.6	2.6	2.6	2.6	2.7	2.7	2.7	2.7	2.8	2.8	2.8	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9
720	2.3	2.6	2.6	2.6	2.7	2.7	2.7	2.7	2.7	2.8	2.8	2.9	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
721	2.5	2.6	2.7	2.6	2.7	2.7	2.7	2.8	2.8	2.8	2.9	2.9	2.9	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
722	2.1	2.3	2.3	2.3	2.3	2.4	2.4	2.5	2.5	2.6	2.6	2.7	2.7	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8
723	2.1	2.2	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.5	2.5	2.5	2.5	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6
724	2.0	2.2	2.2	2.2	2.3	2.3	2.3	2.3	2.4	2.5	2.5	2.6	2.6	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7
725	2.0	2.1	2.2	2.2	2.2	2.3	2.3	2.3	2.4	2.5	2.5	2.5	2.5	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6
726	2.4	2.5	2.5	2.6	2.4	2.4	2.4	2.4	2.5	2.5	2.4	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2
727	2.4	2.6	2.3	DEAD 29 Aug																							
728	2.2	2.4	2.4	2.4	2.4	2.5	2.5	2.5	2.6	2.6	2.6	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7
729	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Phase 3, Toxicological Assessment of ABATE, Study No. 75-51-1302-83, Apr 83

APPENDIX J
SUMMARY OF
RBC CHOLINESTERASE ACTIVITY

Group Treatment	Mean \pm SD RBC Cholinesterase Activity Values (Garry and Routh Units)					
	Pretest	DAY 7 1 Day of Treatment	DAY 10 4 Days of Treatment	DAY 13 7 Days of Treatment	DAY 19 13 Days of Treatment	DAY 30 Sacrifice Day
X Oral Technical ABATE (Mated)	11.9 2.1		8.8* 2.0 t=2.94		4.0* 0.9 t=9.77	5.8* 1.1 t=7.25
XI Oral Technical ABATE (Non-mated)	12.0 1.8		8.7* 1.9 t=4.32		3.8* 0.8 t=14.47	5.9* 1.0 t=10.34
XII Oral 10 percent Acacia (Mated)	12.1 1.4	11.5 1.4 t=1.08		11.8 1.1 t=0.62	13.3 1.7 t=1.73	13.1 2.0 t=1.29
XIII Oral 10 percent Acacia (Non-mated)	11.8 3.2	11.0 2.7 t=0.73		10.9 2.1 t=0.88	11.4 2.2 t=0.46	11.2 2.3 t=0.55

* Significantly lower than pretest value (p<.05)

APPENDIX K

RBC CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)
ABATE, 32 mg/kg/day, ORAL, GROUP X
MATED

Animal Number	Pretest	DAY OF GESTATION		
		Day 10 Test Day 4	Day 19 Test Day 13	Day 30 Sacrifice Day
773	Not Pregnant - Values Disregarded			
774	9.9	7.8	4.5	6.2
775	10.0	8.1	3.5	4.9
776	11.4	9.2	3.1	4.9
777	Not Pregnant - Values Disregarded			
778	Not Pregnant - Values Disregarded			
779	Not Pregnant - Values Disregarded			
780	12.9	7.8	3.8	5.8
781	8.2	6.7	3.3	4.3
782	15.4	13.0	4.5	6.6
783	13.7	11.1	6.0	8.0
784	12.9	8.7	3.5	5.3
785	11.4	6.5	3.0	6.0
786	12.7	9.4	4.4	DEAD
\bar{x}	11.9	8.8	4.0	5.8
$\pm SD$	2.1	2.0	0.9	1.1

APPENDIX L

RBC CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)
ABATE, 32 mg/kg/day, ORAL, GROUP XI
NONMATED

Animal Number	Pretest	DAY OF GESTATION (Equivalent)		
		Day 10 Test Day 4	Day 19 Test Day 13	Day 30 Sacrifice Day
788	11.2	9.1	4.4	5.9
789	15.6	11.6	5.4	7.1
790	14.8	9.3	4.1	7.6
791	11.6	8.5	3.5	4.6
792	10.1	6.9	3.2	4.3
793	10.6	6.5	2.8	DEAD
794	9.4	6.6	3.5	4.7
795	12.6	10.3	4.3	6.1
796	11.3	10.9	4.4	6.6
797	11.7	9.5	4.1	6.5
798	Missed 2 of 4 samples - values disregarded			
799	11.7	8.1	3.0	5.0
800	11.5	5.3	2.6	DEAD
801	14.2	9.5	4.1	6.1
802	11.9	10.2	4.1	6.0
\bar{x}	12.0	8.7	3.8	5.9
\pm SD	1.8	1.9	0.8	1.0

APPENDIX M

RBC CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)
10 PERCENT ACACIA, 0.36 ml/kg/day, ORAL, GROUP XII
MATED

Animal Number	Pretest	DAY OF GESTATION			
		DAY 7 Test Day 1	DAY 13 Test Day 7	DAY 17 Test Day 13	DAY 30 Sacrifice Day
728	10.5	9.5	9.2	10.5	10.4
729	10.8	10.1	11.3	12.1	10.8
730	11.8	11.7	12.5	14.5	12.5
731	Not Pregnant - values disregarded				
732	12.1	12.4	11.5	13.5	12.8
733	10.4	9.1	10.8	11.2	10.6
734	Not Pregnant - values disregarded				
735	11.2	10.5	11.8	15.7	14.6
736	12.9	13.2	12.0	12.3	12.0
737	12.3	11.9	11.8	12.3	14.8
738	15.0	13.2	12.5	14.5	15.8
739	13.4	12.5	13.2	14.1	15.6
740	12.9	12.0	13.0	15.2	13.8
\bar{x}	12.1	11.5	11.8	12.3	13.1
\pm SD	1.4	1.4	1.1	1.7	2.0

APPENDIX N

RBC CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)
10 PERCENT ACACIA, 0.36 ml/kg/day, ORAL, GROUP XIII
NONMATED

Animal Number	Pretest	DAY OF GESTATION (Equivalent)			
		DAY 7 Test Day 1	DAY 13 Test Day 7	DAY 19 Test Day 13	DAY 30 Sacrifice Day
713	18.7	9.9	13.2	12.2	11.7
714	12.1	11.0	11.7	12.2	11.7
715	13.9	13.3	13.2	14.5	13.0
717	14.0	14.5	12.8	13.6	13.7
718	12.7	13.4	12.0	12.2	12.3
719	7.2	7.1	7.9	7.8	8.1
720	7.2	6.9	7.4	7.7	7.1
721	10.2	9.6	9.4	9.3	9.4
722	9.0	8.8	8.3	9.0	8.2
723	11.6	11.1	12.1	13.1	13.7
724	13.5	12.6	12.2	12.2	13.5
725	13.4	15.1	11.8	13.2	12.0
726	10.0	9.4	9.5	10.5	13.4
\bar{x}	11.8	11.0	10.9	11.4	11.2
\pm SD	3.2	2.7	2.1	2.3	2.3

Phase 3, Toxicological Assessment of ABATE, Study No. 75-51-1302-83, Apr 83

APPENDIX 0
SUMMARY OF
PLASMA CHOLINESTERASE ACTIVITY

	Pretest	DAY OF GESTATION					DAY 30 Sacrifice Day
		DAY 7 1 Day of Treatment	DAY 10 4 Days of Treatment	DAY 13 7 Days of Treatment	DAY 19 13 Days of Treatment		
X Oral Technical ABATE (Mated)	5.1 1.2		3.7* 0.8 t=3.08		1.2* 0.4 t=9.33	2.1* 0.5 t=7.09	
XI Oral Technical ABATE (Non-mated)	4.7 0.7		3.2* 0.6 t=5.08		1.2* 0.4 t=15.02	3.4* 0.5 t=5.45	
XII Oral 10 percent Acacia (Mated)	4.4 0.6	4.1 0.6 t=1.00		4.1 0.4 t=1.47	3.7* 0.4 t=3.08	1.9* 0.6 t=10.13	
XIII Oral 10 percent Acacia (Non-Mated)	5.1 0.9	4.9 0.9 t=0.24		4.8 1.1 t=0.13	4.9 1.4 t=0.30	4.4 1.0 t=0.38	

* Significantly lower than pretest value (p<.05)

* Significantly lower than pretest value (p<.05)

APPENDIX P

PLASMA CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)
ABATE, 32 mg/kg/day, ORAL, GROUP X
MATED

Animal Number	Pretest	DAY OF GESTATION		
		DAY 10 Test Day 4	DAY 19 Test Day 13	DAY 30 Sacrifice Day
773	Not Pregnant - values disregarded			
774	5.1	3.9	1.4	1.9
775	3.9	2.8	1.0	1.5
776	5.1	3.0	0.6	2.8
777	Not Pregnant - values disregarded			
778	Not Pregnant - values disregarded			
779	Not Pregnant - values disregarded			
780	5.3	5.3	1.1	2.4
781	7.8	5.2	1.4	2.7
782	4.1	3.0	1.1	1.7
783	6.5	4.8	2.1	1.5
784	4.7	3.7	1.0	1.8
785	4.5	3.6	0.9	2.4
786	4.4	3.7	1.3	DEAD
\bar{x}	5.1	3.7	1.2	2.1
\pm SD	1.2	0.8	0.4	0.5

Phase 3, Toxicological Assessment of ABATE, Study No. 75-51-1302-83, Apr 83

APPENDIX Q

PLASMA CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)
ABATE, 0.32 mg/kg/day, ORAL, GROUP XI
NONMATED

Animal Number	Pretest	DAY OF GESTATION (Equivalent)		
		DAY 10 Test Day 4	DAY 19 Test Day 13	DAY 30 Sacrifice Day
788	6.4	4.4	1.3	3.8
789	4.4	3.3	2.0	3.2
790	5.0	3.2	1.1	3.5
791	4.7	3.3	0.9	3.8
792	4.2	2.8	0.8	2.6
793	4.8	3.2	0.9	DEAD
794	5.0	3.3	0.9	3.7
795	3.7	2.8	1.2	2.9
796	4.5	3.1	1.6	3.2
797	5.1	3.7	1.3	3.9
798	Missed 2 of 4 samples - values disregarded			
799	3.7	2.3	0.7	2.7
800	4.2	2.2	0.7	DEAD
801	4.7	3.1	1.4	3.4
802	5.0	3.6	1.3	3.7
\bar{x}	4.7	3.2	1.2	3.4
$\pm SD$	0.7	0.6	0.4	0.5

APPENDIX R

PLASMA CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)
10 Percent Acacia, 0.36 ml/kg/day, ORAL, GROUP XII
MATED

Animal Number	Pretest	DAY OF GESTATION			
		DAY 7 Test Day 1	DAY 13 Test Day 7	DAY 19 Test Day 13	DAY 30 Sacrifice Day
728	4.4	4.3	3.8	3.4	2.0
729	4.8	3.4	4.2	4.3	2.5
730	3.9	3.5	3.3	3.1	1.3
731	Not Pregnant - values disregarded				
732	4.9	4.7	4.0	3.6	1.6
733	5.4	5.1	4.7	4.5	3.1
734	Not Pregnant - values disregarded				
735	4.4	4.1	4.5	3.3	1.7
736	3.4	3.5	4.0	3.3	1.2
737	4.9	4.8	4.5	3.9	1.5
738	4.5	4.3	4.2	3.9	1.8
739	3.9	4.2	3.8	3.6	2.2
740	3.7	3.5	3.6	3.7	1.5
\bar{x}	4.4	4.1	4.1	3.7	1.9
\pm SD	0.6	0.6	0.4	0.4	0.6

APPENDIX S

PLASMA CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)
10 PERCENT ACACIA, 0.36 ml/kg/day, ORAL, GROUP XIII
NONMATED

Animal Number	Pretest	DAY OF GESTATION (Equivalent)			
		DAY 7 Test Day 1	DAY 13 Test Day 7	DAY 19 Test Day 13	DAY 30 Sacrifice Day
713	5.5	5.0	4.2	4.2	3.6
714	3.6	3.4	3.1	3.4	3.1
715	4.9	4.3	4.5	4.7	2.9
717	5.5	5.5	5.2	5.7	4.4
718	4.4	3.8	2.9	4.0	3.2
719	5.4	5.8	5.8	5.4	4.7
720	6.8	6.6	6.9	7.2	6.4
721	4.4	4.3	4.9	4.8	4.5
722	5.0	4.6	4.8	4.6	4.2
723	4.6	4.3	4.0	4.1	3.6
724	5.6	5.4	5.5	5.1	4.7
725	6.3	5.9	5.8	6.3	5.2
726	4.4	4.1	3.5	4.1	6.0
\bar{x}	5.1	4.9	4.8	4.9	4.4
\pm SD	0.9	0.9	1.1	1.1	1.0

APPENDIX T
SUMMARY OF
MATERNAL BRAIN CHOLINESTERASE ACTIVITY
COMPARISON OF ORAL ABATE-TREATED RABBITS WITH ACACIA CONTROLS

Group	Treatment	Mean \pm SD Brain Cholinesterase Activity Values at End of Study (Day 30 of Gestation) 1:100 Dilution Garry and Routh Units	DF	t
X	Oral Technical ABATE (Mated)	94.3 5.0	9	10.86*
XII	Oral 10 percent Acacia (Mated)	121.2 5.9	11	--

* Significantly lower than control ($p < .05$)

APPENDIX U
SUMMARY OF
NON-MATED FEMALE BRAIN CHOLINESTERASE
ACTIVITY OF ORAL ABATE-TREATED RABBITS WITH
NONMATED ACACIA CONTROLS

Group	Treatment	Mean + SD Brain Cholinesterase Activity		
		Values	at End of Study - Garry and Routh Units	1:100 Dilution
			DF	t
XI	Oral technical ABATE (Non-mated)	92.4 6.1	13	11.40*
XIII	Oral 10 percent Acacia (Non-mated)	127.5 9.2	13	--

* Significantly lower than control ($p < .05$)

APPENDIX V

INDIVIDUAL BRAIN CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)

Group X Oral Technical ABATE Mated		Group XI Oral Technical ABATE Non-Mated		GROUP XII Oral Technical Acacia Mated		GROUP XIII Oral Technical Acacia Non-Mated	
Animal Number	Activity	Animal Number	Activity	Animal Number	Activity	Animal Number	Activity
774	90.5	788	90.4	728	124.0	713	126.2
775	93.1	789	105.3	729	116.7	714	108.0
776	96.0	790	87.1	730	124.5	715	134.3
780	88.5	791	94.2	732	119.4	717	140.5
781	102.1	792	92.1	723	129.5	718	123.6
782	94.4	794	97.8	735	124.5	719	119.2
783	102.1	795	100.4	736	130.2	720	123.6
784	92.6	796	93.7	737	120.6	721	136.0
785	89.4	797	91.4	738	113.0	722	126.5
		798	87.3	739	115.1	723	142.0
		799	82.2	740	115.2	724	122.3
		801	91.6			725	125.7
		802	88.3			726	130.0

APPENDIX W

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